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ORIGINAL ARTICLE
Prevention and epidemiology

Cardiovascular risks associated with calcium supplementation in patients with osteoporosis: a nationwide cohort study

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Aims This study aimed to evaluate the real effects of calcium supplementation on cardiovascular outcomes within a population-based cohort.

Methods and results From a nationwide health screening database in South Korea, a total of 11 297 patients with osteoporosis who had taken calcium supplementation with or without vitamin D for at least 90 days [total calcium group; calcium supplementation only (CaO), $n = 567$; calcium supplementation in combination with vitamin D (CaD), $n = 10\,730$] were matched at a 1:1 ratio to patients who had not taken calcium supplements (control group) by using propensity scores. The overall mean age was 59.9 ± 8.8 years and the percentage of women was 87.9% in our study population. Over a median follow-up of 54 months, the incidence rate of composite cardiovascular diseases (CVDs) per 1000 person-years was not different between the groups: 9.73 in the total calcium group and 8.97 in the control group [adjusted hazard ratio (HR): 1.12; 95% confidence interval (CI): 0.99–1.28; $P = 0.08$]. However, calcium supplementation without vitamin D was associated with an increased risk of composite CVD (HR: 1.54; 95% CI: 1.17–2.04; $P < 0.01$), especially non-fatal myocardial infarction (HR: 1.89; 95% CI: 1.23–2.91; $P < 0.01$), compared with no calcium supplementation.

Conclusion Our population-based study supported that taking calcium supplementation combined with vitamin D did not appear to be harmful to cardiovascular health, but reminded that calcium supplementation without vitamin D should be used carefully even in populations with low dietary calcium intake.

Keywords Calcium • Vitamin D • Cardiovascular disease • Osteoporosis

Introduction

Practice guidelines recommend calcium and vitamin D supplementation for the prevention and treatment of osteoporosis, especially for older patients at high risk of fracture.[1,2] Although these compounds are certainly necessary for bone health, they provide inconclusive results in terms of clinically meaningful reductions in fractures.[3,4] Evidence regarding their impacts on additional anti-fracture efficacy of anti-resorptive agents is still lacking.[5] In the midst of this debate, the adverse effect of calcium supplementation on the cardiovascular system has been a concern since a secondary analysis of the Auckland Calcium Study reported an unexpected warning signal of a higher risk of myocardial infarction (MI) with calcium supplementation.[6,7]

A significant number of studies have not reached consistent conclusions regarding the association between calcium supplementation and cardiovascular events; therefore, applying those results to populations with different backgrounds has been challenging.[8,9] For clarity, large-scale randomized controlled trials (RCTs) with long-term follow-up data are needed, although this seems to be a difficult endeavour.[10] None of the previous large-scale RCTs on calcium supplementation involved primary cardiovascular endpoints.[11–14] On the other hand, existing meta-analyses on this topic have reported

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generally similar findings, suggesting a slight increase in the risk of cardiovascular diseases (CVDs), especially MI, although some were not found to be statistically significant.[15–18] Given the uncertainty, this issue should be clarified using multiple sources. Some epidemiological studies have evaluated this issue with reliable methods; however, most of them were based on Caucasians with moderate to high intake of dietary calcium, which limits the generalizability of their results to other populations with low dietary calcium intake.[7,19] Furthermore, the concomitant use of vitamin D with calcium supplementation should be considered given that vitamin D has possible beneficial effects on the cardiovascular system and that a substantial number of calcium supplement formulations are combined with vitamin D.[20–23]

Therefore, this study aimed to evaluate the association between calcium supplementation and major adverse cardiovascular events among people with osteoporosis in a region with low daily calcium intake. We also assessed the effect of the combined use of vitamin D and calcium supplements on cardiovascular risk.

Methods

Data sources and study cohort

This retrospective propensity-matched cohort study used the Korean National Health Insurance Service Health Screening Cohort (NHIS-HEALS), including 514 866 individuals aged 40–79 years from South Korea. The detailed cohort protocol is presented in the Supplementary material online, *Methods* and has been published previously.[24] This study was approved by the Institutional Review Board (IRB) of Korea University Anam Hospital (IRB number 2019AN0284). Informed consent was waived, because data from the NHIS-HEALS do not involve any personally identifiable data. The process of selecting study participants is summarized in Supplementary material online, *Figure S1*. From the original NHIS-HEALS database, we selected patients with osteoporosis (ICD-10 codes M80–M82) from 1 January 2004 to 31 December 2013. Patients who had been diagnosed with CVDs [non-fatal MI, ischaemic stroke, haemorrhagic stroke, atrial fibrillation (AF), and hospitalization for heart failure] before the index date were excluded. Furthermore, patients who had been hospitalized for osteoporotic fracture within 2 years before the index date, those who had been diagnosed with hypoparathyroidism during the study period, those who had undergone thyroidectomy for thyroid cancer during the study period, and those who had received active vitamin D supplementation were excluded. Patients who had taken calcium supplements with or without vitamin D for at least 3 months were assigned to the total calcium group, while those who had never taken calcium or vitamin D supplements were assigned to the control group. Further subgroups are described in the Supplementary material online, *Methods*.

Study outcomes

The primary outcome was a composite of major adverse cardiovascular events, including non-fatal MI, ischaemic stroke, and death from cardiovascular causes, which were well validated in previous NHIS cohort-based studies.[25] The secondary outcomes were hospitalization for heart failure, AF, and haemorrhagic stroke (Supplementary material online, *Table S1*). Each individual was followed up from the index date to the earliest occurrence of any study outcome, death, or the end of the study period (31 December 2013).

Covariates

Confounding variables included patient age at the index date, sex, body mass index, fasting blood glucose level, total cholesterol level, smoking status (ever or never smoker), alcohol consumption (none, $\leq$2 times per week, or $\geq$3 times per week), physical activity (none, $\leq$2 times per week, or $\geq$3 times per week), socioeconomic status (lowest 30%, middle 40%, or highest 30%), comorbidities (diabetes mellitus, hypertension, and dyslipidaemia), and concurrent medication (antihypertensive agents, statins, antithrombotic agents, and anti-osteoporotic agents) (Supplementary material online, *Table S1*).

Statistical analysis

Data are presented as means and standard deviations for continuous variables or as numbers and percentages for categorical variables. We performed propensity score matching analysis to reduce selection bias and minimize the imbalance in baseline characteristics between the groups. Propensity scores were estimated using a multiple logistic regression model that included all confounding variables in *Table 1*. A total of 11 297 patients who had received calcium supplements (total calcium group) from the case pool (n = 14 733) were matched in a 1:1 ratio with 11 297 patients who had never received calcium and vitamin D supplements (control group) from the control pool (n = 14 958) (Supplementary material online, *Figure S1*). Matching performance was evaluated using the absolute standardized difference of variables used for matching patients from the total calcium group and the control group. For each group, the incidence of each outcome with its 95% confidence interval (CI) was calculated per 1000 person-years. A stratified Cox proportional hazards regression model for matched data was used to evaluate the relative hazard for events in the calcium groups [total calcium, calcium-only supplementation (CaO), and calcium supplementation in combination with vitamin D (CaD) groups] considering the control group as reference; the relative hazards are presented as the hazard ratio (HR) and its 95% CI. When each calcium group (CaO or CaD) was compared with the control group, we further readjusted for variables that were significantly different between the groups. The same analysis was also performed for calcium intake from supplementation, with its cumulative dose and cumulative treatment duration used as time-dependent covariates. Furthermore, restricted cubic spline Cox regression was performed to predict the continuous relationship between the daily mean dose of calcium from supplementation and cardiovascular outcomes using four knots placed at 5, 35, 65, and 95 percentiles of the cumulative average of calcium. Further information about statistical analysis is presented in the Supplementary material online, *Methods*.

SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses, and a two-sided P-value $<$0.05 was considered statistically significant.

Results

Baseline characteristics

After propensity score matching, the baseline characteristics of the calcium and control groups were well balanced with absolute standardized differences of $<$0.1 (*Table 1* and Supplementary material online, *Figure S2*). The overall mean age of our study population was 59.9 $\pm$ 8.8 years and 87.9% were female. In the total calcium group, the mean calcium dose was 537.8 mg, and the mean duration of calcium intake from supplementation was 22.6 months. Among 11 297 patients who had taken calcium

Table 1 Baseline characteristics according to propensity score matching

Characteristics	Control group ($n = 11\,297$)	Calcium (± vitamin D) group ($n = 11\,297$)	Absolute standardized difference[a]	
			Before matching	After matching
Mean (SD) age (years)	59.9 (9.3)	60.0 (8.3)	0.01	0.02
Men, *n* (%)	1371 (12.1)	1355 (12.0)	0.05	0.02
Mean (SD) body mass index	23.7 (3.0)	23.7 (3.0)	0.09	0.01
Mean (SD) systolic blood pressure (mmHg)	124.3 (16.5)	124.2 (16.3)	0.14	<0.01
Mean (SD) fasting glucose (mmol/L)	5.4 (1.5)	5.3 (1.2)	0.05	0.02
Mean (SD) total cholesterol (mmol/L)	5.3 (1.0)	5.3 (1.0)	0.03	0.03
Ever smoker, *n* (%)	1227 (10.9)	1258 (11.1)	0.33	0.01
Alcohol consumption, *n* (%)			0.21	0.01
None	9507 (84.2)	9452 (83.7)		
≤2 times/week	1364 (12.1)	1406 (12.5)		
≥3 times/week	426 (3.8)	439 (3.9)		
Regular exercise, *n* (%)	8001 (70.8)	8167 (72.3)	0.08	0.03
Socioeconomic status, *n* (%)			0.08	0.02
Lower 30%	2720 (24.1)	2690 (23.8)		
Middle 40%	3749 (33.2)	3671 (32.5)		
Upper 30%	4831 (42.8)	4936 (43.7)		
Comorbidities, *n* (%)				
Diabetes mellitus	1020 (9.0)	1013 (9.0)	0.02	<0.01
Hypertension	3676 (32.5)	3693 (32.7)	0.08	<0.01
Dyslipidaemia	2425 (21.5)	2395 (21.2)	0.19	<0.01
Concurrent drug treatment, *n* (%)				
ARB/ACE inhibitors	1730 (15.3)	1865 (16.5)	0.12	0.03
β-Blockers	1436 (12.7)	1486 (13.2)	0.12	0.01
CCB	733 (6.5)	761 (6.7)	0.05	0.01
Diuretics	1973 (17.5)	2055 (18.2)	0.14	0.02
Statins	2292 (20.3)	2263 (20.0)	0.31	<0.01
Antithrombotic agents	5320 (47.1)	5432 (48.1)	0.45	0.02
Daily calcium dose, mean (SD), mg/day	—	537.8 (245.4)		
Duration of calcium treatment, *n* (%)				
3–6 months		2490 (22.0)		
6–12 months		2404 (21.3)		
>12 months		6403 (56.7)		

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; CCB, calcium channel blocker; SD, standard deviation.
[a] Absolute standardized differences comparing baseline covariates between the total calcium group and the control group.

supplements, 567 (5%) patients who were treated with calcium supplementation only were included in the CaO group and 10 730 (95%) patients who were treated with calcium plus vitamin D supplementation were included in the CaD group (Supplementary material online, *Table S2*). Patients in the CaO group had more cardiovascular risk factors, including older age, higher systolic blood pressure, and ever-smoking status, than those in the CaD group (all $P < 0.05$).

Risk of major adverse cardiovascular events

Table 2 shows the incidence rates (per 1000 person-years) and HRs of major adverse cardiovascular events in the calcium and control groups. During the median follow-up of 54 months (interquartile range: 30–78 months), 525 and 487 cardiovascular events occurred in the total calcium and control groups, respectively. Calcium supplementation did not increase the risk of composite cardiovascular events (HR: 1.12; 95% CI: 0.99–1.28). The risks of non-fatal MI (HR: 1.20; 95% CI: 0.96–1.49), ischaemic stroke (HR: 1.11; 95% CI: 0.94–1.32), and death due to cardiovascular causes (HR: 0.81; 95% CI: 0.51–1.29) were not different between the groups (Supplementary material online, *Figure S3*).

However, calcium supplementation without vitamin D (CaO group) was associated with a significantly increased risk of composite cardiovascular events (HR: 1.54; 95% CI: 1.17–2.04) compared with no calcium supplementation (control group). The risk of non-fatal MI was also higher (HR: 1.89; 95% CI: 1.23–2.91) in the CaO group than in the control group (*Figure 1*). In contrast, the

Table 2 Risk of major adverse cardiovascular events

Study outcomes	Control group (*n* = 11 297)	Calcium groups: Total (*n* = 11 297)	*P*-value[a]	CaO (*n* = 567)	*P*-value[b]	CaD (*n* = 10 730)	*P*-value[b]
Composite CVD events							
Number of events	487	525		57		468	
Incidence per 1000 person-years	8.97 (8.21–9.80)	9.73 (8.94–10.60)		18.70 (14.43–24.25)		9.20 (8.40–10.07)	
Hazard ratio (95% CI)	1.00 (ref)	1.12 (0.99–1.28)	0.08	1.54 (1.17–2.04)	<0.01	1.12 (0.98–1.28)	0.11
Non-fatal myocardial infarction							
Number of events	173	198		24		174	
Incidence per 1000 person-years	3.14 (2.71–3.65)	3.61 (3.14–4.15)		7.66 (5.13–11.43)		3.37 (2.90–3.90)	
Hazard ratio (95% CI)	1.00 (ref)	1.20 (0.96–1.49)	0.11	1.89 (1.23–2.91)	<0.01	1.13 (0.90–1.42)	0.30
Ischaemic stroke							
Number of events	291	313		31		282	
Incidence per 1000 person-years	5.31 (4.73–5.96)	5.75 (5.14–6.42)		9.93 (6.98–14.12)		5.49 (4.89–6.17)	
Hazard ratio (95% CI)	1.00 (ref)	1.11 (0.94–1.32)	0.23	1.33 (0.91–1.95)	0.13	1.12 (0.94–1.33)	0.20
Cardiovascular deaths							
Number of events	46	38		5		33	
Incidence per 1000 person-years	0.83 (0.62–1.11)	0.69 (0.50–0.94)		1.56 (0.65–3.74)		0.63 (0.45–0.89)	
Hazard ratio (95% CI)	1.00 (ref)	0.81 (0.51–1.29)	0.37	0.94 (0.33–2.61)	0.90	0.96 (0.57–1.60)	0.86

CaO, calcium only; CaD, calcium plus vitamin D; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; ref, reference.
[a] The *P*-value for comparing the total calcium group with the control group was obtained by stratified Cox proportional hazards regression analysis with further adjustment for the use of anti-osteoporotic agents.
[b] The *P*-value for comparing the CaO or CaD group with the control group was obtained by multiple Cox proportional hazards regression analysis after adjusting for age, sex, body mass index, systolic blood pressure, fasting blood glucose level, total cholesterol level, smoking status, alcohol intake, level of physical activity, socioeconomic status, comorbidities, concurrent drug treatment, and use of anti-osteoporotic agents.

CaD group showed no increase in the risk of major adverse cardiovascular events compared with the control group (HR: 1.12; 95% CI: 0.98–1.28).

Risk of major adverse cardiovascular events according to the duration and dose of calcium supplementation

Given that calcium supplementation without vitamin D has been associated with an increased risk of cardiovascular events, we investigated a possible dose-dependent relationship between calcium-only supplementation and cardiovascular risk. Compared with no calcium supplementation (control group), calcium-only supplementation (CaO group) at the highest daily dose (≥1000 mg) (HR: 1.92; 95% CI: 1.13–3.25) and that for the longest duration (≥12 months) (HR: 1.96; 95% CI: 1.32–2.93) were significantly associated with an increased risk of composite cardiovascular outcomes (*Table 3*). However, these relationships were not observed in the CaD group. The spline curves for the relationship between the daily average dose of calcium and cardiovascular risk also showed different patterns in the CaO and CaD groups (*Figure 2*).

Subgroup analysis for the risk of composite cardiovascular events

Figure 3 shows the results of subgroup analyses of the association between calcium supplementation and composite CVD events in the CaO group. No significant interactions were found between calcium supplementation and all stratified variables (all *P* for interaction >0.05), except for treatment with a calcium channel blocker. The HR of composite CVD events was higher in patients taking a calcium channel blocker and calcium supplements than in those taking a calcium channel blocker but not calcium supplements (HR: 3.38; 95% CI: 1.87–6.12). In the CaD group, there were no significant interactions between calcium supplementation and all stratified variables (all *P* for interaction >0.05; Supplementary material online, *Figure S4*).

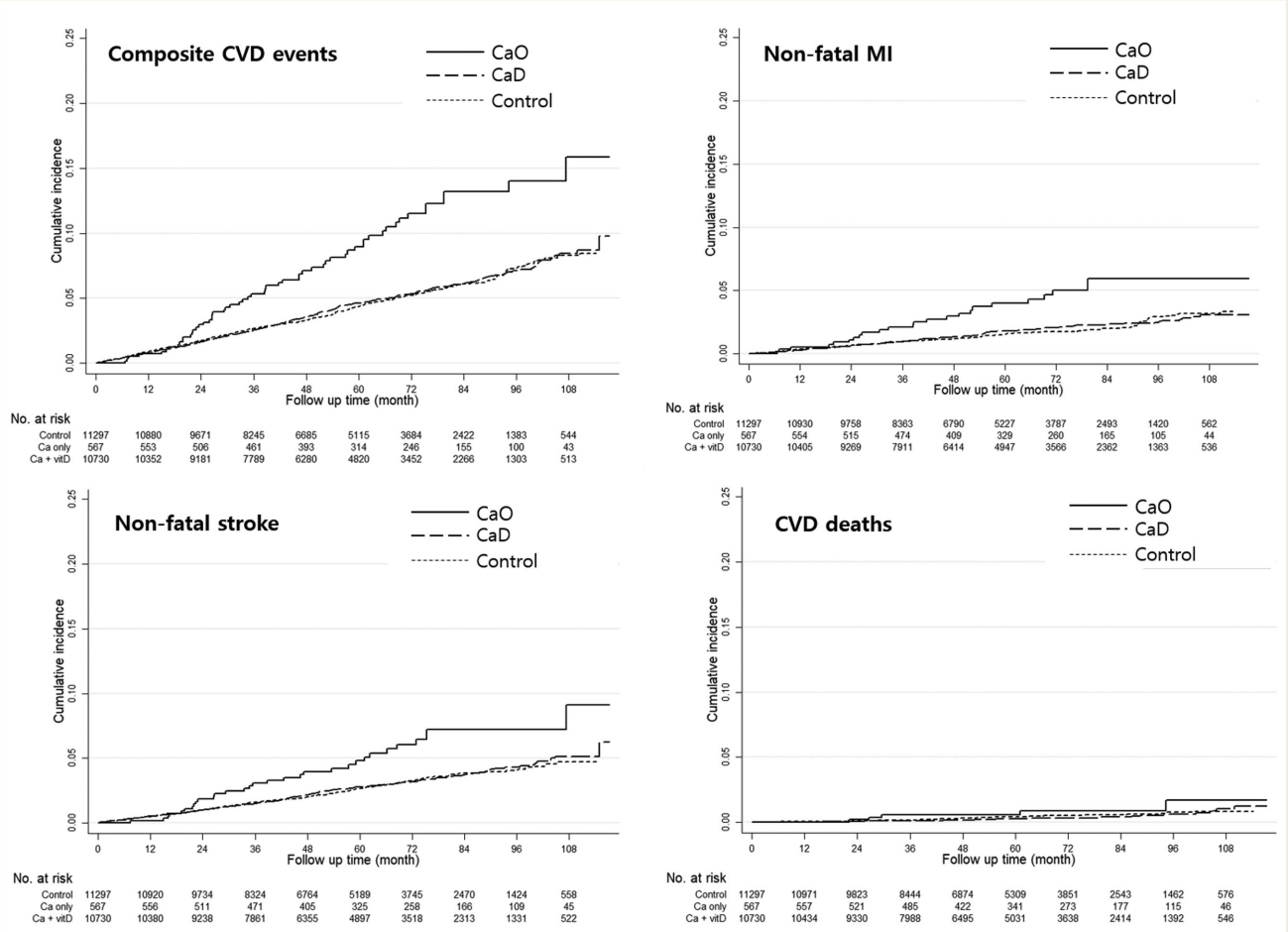

Figure 1 Kaplan–Meier survival curves for composite cardiovascular events in the total calcium group with the control group used for comparison.

Discussion

In this propensity-matched cohort study including people diagnosed with osteoporosis without established CVD, calcium supplementation was not associated with an increased risk of major cardiovascular events. However, the results differed depending on whether vitamin D was concomitantly used or not. Calcium supplementation without vitamin D, especially at a high dose (≥1000 mg) or for a long duration (≥12 months), was associated with a higher risk of composite CVD events, while the combined use of calcium and vitamin D did not show an increased risk of CVD.

Osteoporosis is a metabolic bone disease characterized by low bone mass and decreased bone quality, with a consequent increase in fracture risk.[26] Osteoporotic fracture has become one of the major healthcare problems leading to reduced quality of life and high mortality, especially in elderly patients.[27] Therefore, preventing and managing osteoporosis and osteoporotic fractures are important.[27] Calcium supplementation has been widely used in most patients with osteopenia or osteoporosis, especially elderly patients at high risk of fractures.[2] In this regard, there has been a need for stronger evidence to confirm the cardiovascular safety of calcium supplementation.[9] Although the mechanism underlying the increased CVD risk with calcium supplementation is not fully understood, there have been several speculations.[28] First, serum calcium levels rapidly increase after the ingestion of calcium supplements, resulting in accelerated vascular calcification.[29] Updated Mendelian randomization analysis also supports this by showing causal evidence for harmful effects of genetically elevated serum calcium levels related to CVD, especially MI.[30,31] Second, both clot initiation and clot strength are associated with hypercalcaemia in humans owing to the importance of calcium in the coagulation pathway with respect to calcium-sensing receptors.[32] Recent studies have shown that calcium supplementation over 5 years or after 10 years of follow-up increased the risk of coronary artery calcification.[33,34] Coronary intravascular ultrasound as a highly sensitive imaging modality for detecting volumetric plaque changes also further demonstrated progressive arterial calcification in patients receiving calcium supplementations.[35] Previous meta-analyses were in line with the above hypothesis reporting that patients taking calcium supplements had an ~20% increased incidence of MI compared with those taking placebos.[17,18] Yang *et al.* also reported increased risk of coronary artery disease with calcium supplementation with or without vitamin D by 8%, which was

Table 3 Risk of composite cardiovascular outcomes associated with the daily dose and duration of calcium and/or vitamin D supplementation

	n	Incidence (per 1000 person-years)	No. of events	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Total calcium group					
Control	11 297	8.97 (8.21–9.80)	487	Reference	Reference
Daily average dose of calcium					
<500 mg	4416	9.77 (8.52–11.20)	206	1.08 (0.92–1.28)	1.08 (0.91–1.27)
500–1000 mg	5185	8.60 (7.52–9.840)	211	0.96 (0.81–1.12)	0.97 (0.82–1.14)
≥1000 mg	857	11.99 (8.95–16.05)	45	1.34 (0.99–1.82)	1.29 (0.95–1.74)
Duration of calcium supplementation[b]					
<6 months	11 297	10.51 (9.01–12.25)	163	1.19 (0.99–1.42)	1.15 (0.96–1.37)
6–12 months	8807	9.67 (8.18–11.44)	136	1.08 (0.90–1.31)	1.04 (0.86–1.26)
≥12 months	6403	9.27 (8.14–10.57)	226	1.02 (0.87–1.19)	1.05 (0.89–1.23)
Daily average dose of vitamin D					
<800 IU	5589	8.55 (7.52–9.71)	235	0.95 (0.81–1.11)	0.98 (0.83–1.14)
≥800 IU	5125	9.79 (8.60–11.14)	228	1.09 (0.93–1.27)	1.07 (0.92–1.26)
CaO group					
Control	11 297	8.97 (8.21–9.80)	487	Reference	Reference
Daily average dose of calcium					
<500 mg	146	17.14 (10.33–28.42)	16	1.87 (1.11–3.14)	1.47 (0.87–2.47)
500–1000 mg	265	19.09 (12.09–28.25)	15	2.12 (1.41–3.16)	1.39 (0.93–2.08)
≥1000 mg	138	19.13 (11.33–32.29)	26	2.11 (1.25–3.57)	1.92 (1.13–3.25)
Duration of calcium supplementation[b]					
<6 months	567	13.91 (8.52–22.71)	16	1.61 (0.98–2.65)	1.42 (0.86–2.35)
6–12 months	389	17.17 (10.35–28.48)	15	1.97 (1.18–3.29)	1.25 (0.74–2.11)
≥12 months	236	25.39 (17.29–37.30)	26	2.80 (1.89–4.15)	1.96 (1.32–2.93)
CaD group					
Control	11 297	8.97 (8.21–9.80)	487	Reference	Reference
Daily average dose of calcium					
<500 mg	4270	9.45 (8.20–10.89)	191	1.05 (0.89–1.24)	1.15 (0.97–1.38)
500–1000 mg	4920	8.01 (6.94–9.25)	186	0.89 (0.75–1.05)	1.01 (0.84–1.20)
≥1000 mg	719	10.26 (7.21–14.58)	31	1.15 (0.80–1.66)	1.22 (0.84–1.76)
Duration of calcium supplementation[b]					
<6 months	10 730	10.24 (8.71–12.03)	147	1.16 (0.96–1.39)	1.23 (1.02–1.49)
6–12 months	8418	9.18 (7.68–10.97)	121	1.03 (0.84–1.25)	1.12 (0.91–1.38)
≥12 months	6167	8.57 (7.46–9.84)	200	0.94 (0.79–1.11)	1.09 (0.92–1.29)
Daily average dose of vitamin D					
<800 IU	5589	8.55 (7.52–9.71)	235	0.95 (0.81–1.11)	1.05 (0.90–1.24)
≥800 IU	5125	9.79 (8.60–11.14)	228	1.09 (0.93–1.27)	1.17 (0.99–1.38)

CaO, calcium only; CaD, calcium plus vitamin D; CI, confidence interval; HR, hazard ratio.
[a] Calculated by multiple Cox proportional hazards regression analysis adjusted for age, sex, body mass index, systolic blood pressure, fasting blood glucose level, total cholesterol level, smoking status, alcohol intake, level of physical activity, socioeconomic status, comorbidities, concurrent drug treatment, and use of anti-osteoporotic agents.
[b] Using time-dependent Cox proportional hazards regression analysis.

deteriorated with higher risk of coronary artery disease by 20% when calcium supplementation alone was taken.[8] Moreover, their dose–response analysis concerned taking calcium intake higher than 1000 mg/day with increasing risk of coronary heart disease. These findings support our results of a higher risk of CVD with calcium supplementation alone, especially at the highest dose (≥1000 mg) or for the longest duration (≥12 months). Therefore, when calcium supplementation alone is used, the elemental calcium dose should be restricted up to 1000 mg/day for cardiovascular safety.

The different effects on cardiovascular health caused by the formulation of calcium intake need to be clarified. Contrary to the supplemental form, dietary calcium intake has been reported as decreasing risks of CVD according to previous studies.[8,36] Transient hypercalcaemia caused by calcium supplementation might be a reason, while dietary calcium intake did not show prominent change of serum calcium level.[37] Dairy products are composed of calcium hydroxyapatite that is more incorporated into bones, which have less impact on the level of serum calcium. However, calcium

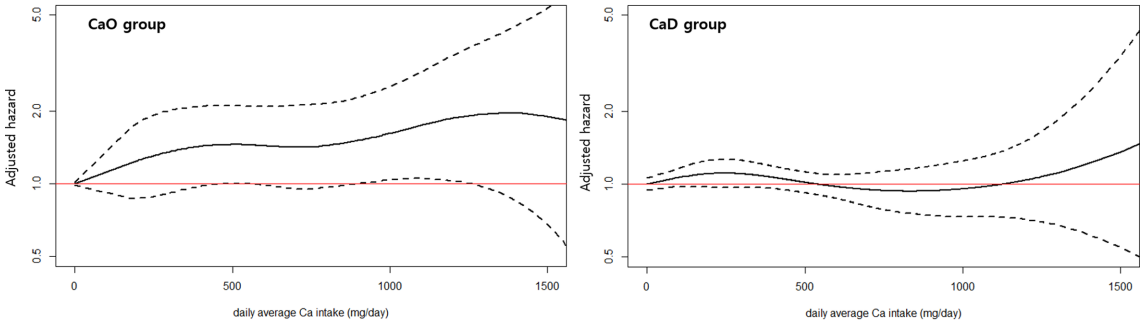

Figure 2 Multivariable adjusted spline curves for the relationship between average calcium supplement dose and the time to events.

supplements mainly containing calcium salts can increase serum calcium acutely.[38] Yang *et al.* also supported the hypothesis that there was no association between dietary calcium intake and the risk of CVD.[8]

However, calcium supplementation in the total calcium group did not appear to increase the risk of CVD in our study. The difference between our results and those of previous studies performed in Caucasians may be explained by the characteristics of our study population with a low calcium intake.[19,39] A study from the Korea National Health and Nutrition Examination Survey reported that the mean daily calcium intake was only 490 mg/day in Koreans, which is much lower than that in Caucasians.[19,40] Thus, low calcium intake in the Korean population may have resulted in underestimation of the cardiovascular risk related to calcium supplementation in this study. Another explanation of our neutral outcome involves the differential effects of calcium supplementation alone and calcium supplementation with vitamin D, which were discussed in several studies.[8,23,41] Coadministration of vitamin D with calcium supplementation in most patients in our study might be a crucial factor for the attenuation of the cardiovascular risk of calcium supplementation alone. Evidence has demonstrated a link between decreased vitamin D levels and CVD, supporting the cardioprotective role of vitamin D supplementation.[42] Vitamin D can protect vessel walls against atherosclerosis by increasing the expression of anti-inflammatory cytokines, decreasing the expression of pro-inflammatory molecules, and down-regulating plaque-destabilizing enzymes.[43] Notably, the prevalence of vitamin D deficiency (defined as the serum 25(OH)D level of <20 ng/ml), a well-known risk factor for CVD, has been increasing in South Korea, reaching 75.2% in men and 82.5% in women.[44] Considering these findings together, combined vitamin D and calcium supplementation in our patients, who were assumed to have severe vitamin D deficiency, may have led to better outcomes than those expected in other populations. Except for cardiovascular outcomes, there has been little evidence evaluating the differential effect of calcium supplements alone or in combination with vitamin D. Several studies compared the difference of vitamin D between with and without calcium supplements regarding non-cardiovascular effects.[45,46] Vitamin D with calcium supplements had beneficial effects on hip fracture and mortality compared with vitamin D alone. Their interaction can be explained by the different degrees of calcium absorption based on heterogeneous status of mineral metabolism and various study designs.[47]

Interestingly, the HR of composite CVD was significantly higher in participants who take calcium supplements and calcium channel blockers at the same time in our subgroup analysis. The effect of combination treatment with these drugs on the cardiovascular system has not yet been elucidated.[48,49] According to Civantos *et al.*, calcium supplements can antagonize the effect of the calcium channel blockers in older rats (20- and 25-week-old spontaneously hypertensive rats), showing that concomitant use of calcium-enriched diet and amlodipine increased blood pressures higher than those of rats taking normal calcium diet with amlodipine.[50] However, there has been little evidence studying humans about this issue so far, and further research may be warranted to validate the findings.

The present study has several strengths. First, the number of patients was high, providing sufficient statistical power. Second, we used the propensity score matching method to reduce any imbalance between the calcium-treated and untreated groups by reflecting real clinical practice. We also considered a wide range of variables as covariates that affect CVD risk, including demographic and socioeconomic characteristics, biochemical data, comorbidities, and concurrent medication. Additionally, a detailed analysis was conducted according to the exposure–response relationship between calcium and vitamin D in terms of dose and duration. However, this study also had some limitations that warrant discussion. First, we could not consider information about the real calcium intake of each patient because this database did not include nutritional information such as data on dietary calcium intake or additional calcium supplementation not covered by the NHIS. However, a well-designed study reported that the mean daily calcium intake in the general South Korean population was lower than that in other ethnic groups.[19] A recent study also announced that most Koreans have not taken health supplements including calcium and vitamin D.[44] Therefore, the difference in unrevealed calcium intake from supplementation between the two groups is unlikely to have affected the results. Second, data on serum vitamin D and calcium levels were not available in this NHIS-HEALS cohort. Therefore, the baseline status of mineral deficiency could not be considered. Third, the possibility of residual confounding factors including medication adherence cannot be

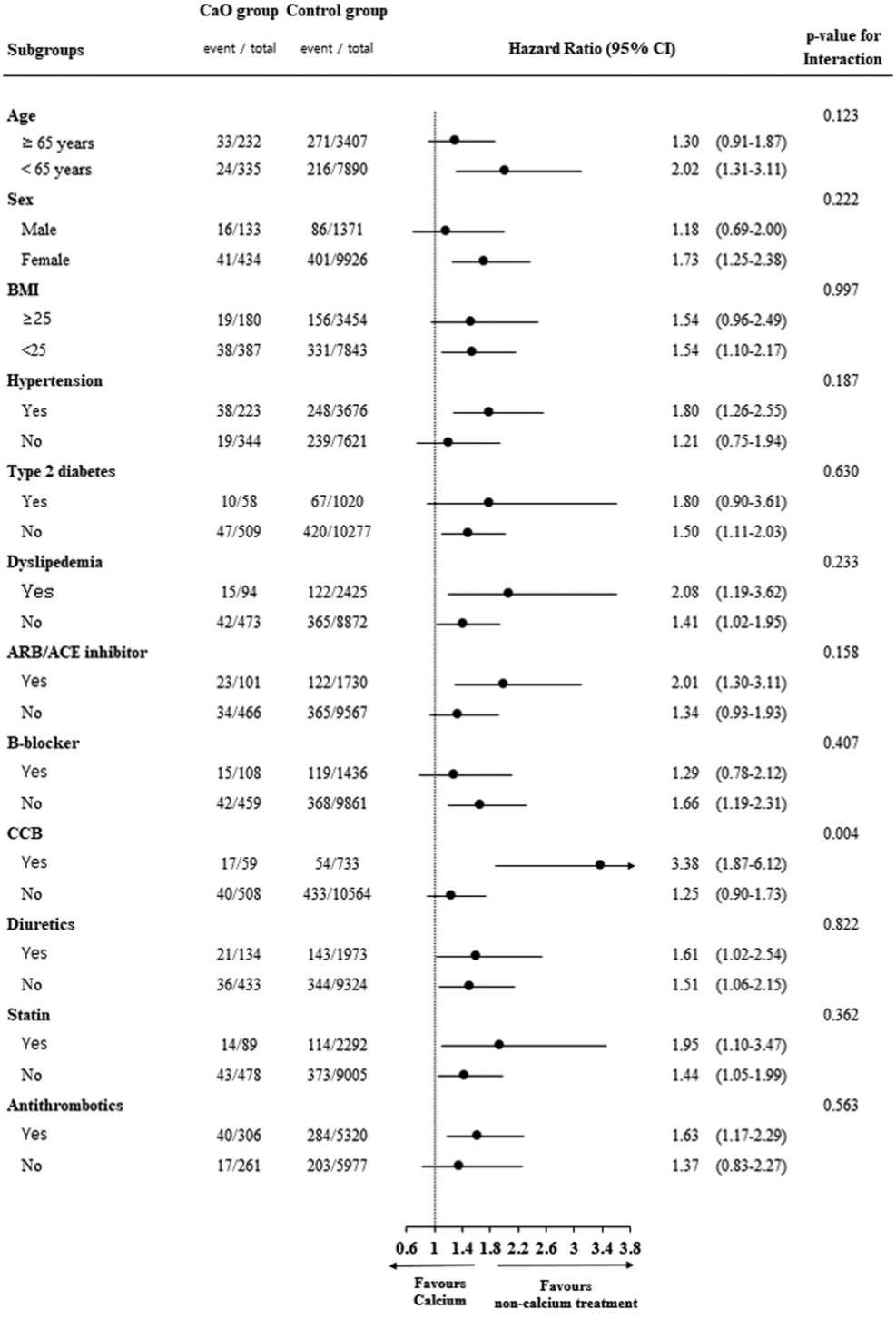

Figure 3 Subgroup analysis of the incidence of composite cardiovascular events in the calcium-only supplementation group with the control group used for comparison.

excluded, although we adjusted for diverse variables. Lastly, caution should be taken when generalizing our results to other populations because our study only included part of Koreans, not even whole Koreans due to the design of cohort;[24] we also excluded those with diseases related to previous CVD and mineral metabolism, such as chronic kidney disease and parathyroid disease, at baseline. However, the use of these selection criteria allowed the creation of homogeneous populations and reduced confounding bias.

Conclusions

We found that calcium supplementation with vitamin D did not increase the risk of CVD among patients with osteoporosis without baseline CVD. This result reflects a real-world setting, where calcium supplementation is usually prescribed with vitamin D supplementation. However, taking calcium supplements alone without vitamin D supplements was associated with an increased risk of CVD, especially non-fatal MI, even among populations with low calcium intakes, such as the Korean population. Therefore, our study confirms the cardiovascular safety of calcium supplements with vitamin D, but excess calcium supplements without vitamin D are associated with a potential risk of CVD.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

Data sets are available through approval and oversight by the Korean National Health Insurance Service. Statistical code: see Supplementary material online.

Conflict of interest: None declared.

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